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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,049	11/01/2005	Eva Kontsekova	SONN:066US	5434

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/17/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,049	KONTSEKOVA ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C: § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Status of claims. Claims 17-33 are pending. Claims 17 and 25 have been amended by Applicants amendment filed on 01-10-2007. Currently, claims 17-33 are pending for examination.
3. The examiner acknowledges receiving the Declaration under 37 C.F.R. § 1.132 signed by Dr. Peter Filipcik.

Response to arguments

Withdrawn rejections in response to Applicant arguments or amendments:

Claim objections

In response to Applicants amendment of claim 17 to clarify that it is the "cDNA molecule" that is truncated at least 30 nucleotides downstream of the star codon, objection of Claim 17 is withdrawn.

Claim Rejections - 35 USC § 112- Second paragraph

In response to Applicants amendment of claim 17 to delete the phrase "minimally truncated tau core", rejections of claim 17 under 35 U.S.C. 112, second paragraph, has been withdrawn.

In response to Applicants amendment of claim 25 to include the following step : administering the candidate to a non-human transgenic animal of claim 17, rejections of claims 25 and dependent claims 26 and 27 under 35 U.S.C. 112, second paragraph, has been withdrawn.

Remaining objections/ rejections in response to Applicant arguments or amendments:

Claim Rejections - 35 USC § 112 – enablement

In view of the Declaration under 37 C.F.R. § 1.132 signed by Dr. Peter Filipcik teaching the generation of the transgenic rat line #318 which is the same transgenic rat disclosed in the as-filed specification (page 22, paragraph 2) and the characterization of said transgenic rat # 318 phenotype in the post filling publication by Zilka et al., (Truncated tau from sporadic Alzheimer's disease suffices to drive neurofibrillary degeneration in vivo, 2006, FEBS Letters 580:3582-3588) filed on 01-10-2007, as exhibit 2 , rejection of claims 17-33 under 35 U.S.C. 112, first paragraph, has been modified to the following enablement scope.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

A transgenic rat whose genome comprises a transgene comprising a DNA construct encoding a N- and C-terminally truncated human tau protein of SEQ ID No. 9, said DNA operably linked to a promoter, wherein the promoter is a mouse Thy-1 promoter, wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology occurs in the rat when compared to normal rats,

The specification does not enable any person skilled in the art to which it pertains or with which it is most nearly connected, to use the invention commensurate in scope with this claim. Claims 17-33 remain rejected for the reasons of record.

Reply to applicant arguments as they relate to rejection of Claims 17-33 under 35 U.S.C. 112, first paragraph, scope of enablement.

On page 3, the Filipcik Declaration states "the truncated tau protein numbered amino acids 151-391 in the Zilka reference is the same as a truncated tau protein numbered amino acids 93-333 based on the numbering in the patent application. Using the numbering in the patent application, amino acids 93-333 correspond to nucleotides 279-999. Thus, the truncated tau cDNA molecule used to generate rat line #318 is truncated at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full-length tau cDNA sequence coding for 4-repeat and 3-repeat tan protein; and the truncated tau cDNA molecule comprises SEQ ID NO: 9 (nucleotides 741-930)". On pages 8 and 9 of Applicants Remarks, Applicant refers to the Filipcik Declaration above to teach support for enablement of amended claim 17. Such is not persuasive.

The Declaratory evidence is not commensurate in scope with the claims but only with only commensurate with the identified scope of enablement . The scope of the invention as embraced by claim 17 and its remaining dependent claims is not commensurate with the disclosure of the as filed evidence for the reasons of record and the following reasons: amended claim 17, can broadly be interpreted as any cDNA construct encoding for truncated tau molecules presented as schematic diagrams in Fig. 1 of truncated tau molecules constructs and identified as SEQ ID Nos: 3, 6-9, 12, and 14 that are embraced by amended claim 17, including nucleotide residues 741-930 (Fig. 1, SEQ ID No. 9) the instant claim. However, there is no disclosure about the effect of these truncated tau proteins on the assembly of microtubule other than for SEQ ID No. 9 used to generate the transgenic line #318. Further, the instant specification fails to teach which specific encoded amino acids to be substituted, deleted or inserted within the minimally truncated tau core of at least 30 nucleotides downstream of the start codon and at least 30 nucleotides upstream the stop codon of the full length tau cDNA sequence, at which positions and in which combinations such that the encoded polypeptide derivative for N- and C-terminally truncated tau gene is still functional to yield neurofibrillary degeneration contemplated by Applicants results. Hence, the Declaratory evidence is not commensurate in scope with the claims

On page 10 of applicant remarks, Applicants argue that transgenic Tau proteins of the present invention are associated with useful phenotypes and quotes the Zilka reference on p. 3585, to support the association of the expression of truncated tau proteins as encoded by a cDNA of the invention with useful phenotypes. Such is not persuasive.

While the instant specification teaches that transgene expression was detected for expression Alzheimer's tau proteins in the brain of transgenic rat #318 by Western analysis and corresponding proteins were localized by immunohistochemistry tissue sections, and Alzheimer's like neurofibrillary pathology was observed, the instant claims can be broadly interpreted as useful models for any Alzheimer's pathology including hypertension, diabetes, hypercholesterolemia, and a variety of neurobehavioral symptoms. The instant specification is completely silent in this regard, let alone the nexus on the etiology of neurofibrillary pathology in humans and murine models in relation to a functional pathology. In other words, are the gene mutations in humans resulting in Alzheimer's pathologies the same as in the transgenic truncated tau protein model? . Similarly, there is no correlation for association between expression of any derivative of the Alzheimer's tau proteins in rat with any relevant characteristics or useful phenotype other than neurofibrillary pathology. Though the Zilka reference states "in human sporadic Alzheimer's pathology, mature neurofibrillary degeneration is characterized by extensive formation of sarcosyl insoluble tau protein complexes" (p. 3587, col. 1, last paragraph), the same inventor contends that the observed pathological changes are just one of the multiple factors in the Alzheimer's disease by stating "The present study provides the experimental data introducing truncated tau protein as an important upstream factor in the pathogenesis of neurofibrillary degeneration of AD type" (p. 3587, col. 2, last paragraph).

On page 12 of applicant remarks, Applicants contend that none of the references cited by the examiner in the previous office action "discuss the expression of tau proteins as described in the present application, and are instead drawn toward general aspects of transgenic science or

descriptions of transgenic models of specific diseases that are unrelated to Alzheimer's disease". Moreover, Applicant provides the following references to support of the enablement of the instant claims as examples of transgenie science, wherein the expression of identical or homologous gene constructs in different animals results in those animals exhibiting similar phenotypes: "Gurney et al., Science 264:1772-74 (1994) and Howland et al., PNAS 99:1604-09 (2002) (transgenic expression of the same mutated superoxide dismutase in mice and in rats resulted in nearly the same phenotype); von Horsten et al., Human Mol. Gen. 12:617-24 (2003); Bates et al., Human Mol. Gen. 6:1633-37 (1997); Mangiarini et al., Cell 87:493-506 (1996) (animal modeling of Huntington's disease in mice and rats found to be comparable) (Exhibits 4-8, respectively)". Such is not persuasive.

The references filed on 01-10-2007 as exhibits by Applicants are examples of transgenic mice expressing a very specific phenotype (e.g., amyotropic lateral sclerosis, ALS), said transgenic phenotype related to the human phenotype wherein the same gene is mutated, for example, Gurney et al., Science 264:1772-74 (1994, teach that transgenic expression of the mutated superoxide dismutase in mice resulted in motor neuron disease and Howland et al., PNAS 99:1604-09 (2002) teach that transgenic overexpression of superoxide dismutase, linked to inheritance in an autosomal dominant genetic mutation in human ALS, resulted in early transgenic onset of disease and ultimately death. Similarly, the von Horsten et al., Human Mol. Gen. 12:617-24 (2003), Bates et al., Human Mol. Gen. 6:1633-37 (1997), and Mangiarini et al., Cell 87:493-506 (1996) references disclose the use of transgenic rat models in studies of Huntington's disease (HD), which is a genetic autosomal dominant disorder wherein mutation of an expanded and unstable CAG trinucleotide repeat within the coding region of the HD, causes

progressive degeneration of neurons. Hence the instant references are enabling for transgenic murine models with specific truncations of genes resulting in a specific phenotype. However, none of the cited references filed on 01-10-2007 by Applicants are examples of correlation between expression of any Alzheimer's tau proteins in rat with any useful phenotype (e.g., hypertension, diabetes, hypercholesterolemia) other than neurofibrillary pathology. Further, post-filing art by Hrnkova M et al., (Brain Res. 2007, 1130 :206-13) teaches a lack of nexus betwenn transgenic rats with human truncated tau protein and any Alzheimer's disease. The results of the Hrnkova M et al., study merely suggest that "neurodegeneration, caused by the non-mutated human truncated tau derived from sporadic human AD, result in the neuronal dysfunction consequently leading to the progressive neurobehavioral impairment" (p. 209, col. 2, paragraph 1). In view of the studies discussed above, there is no correlation for association between expression of any derivative of the Alzheimer's tau proteins in rat with any Alzheimer's pathology as embraced by the amended claim 17 other than a transgenic rat whose genome comprises a transgene having a DNA sequence encoding a N- and C-terminally truncated human tau protein of SEQ ID No. 9, wherein said truncated tau protein is expressed in the rat brain and neurofibrillary pathology occurs.

On page 14 of Remarks, Applicants cite specific pages and paragraphs for the following disclosed information: the preparation of constructs of the present invention and their injection into male pronuclei of one-day old rat embryos via microinjection, genotyping of animals born after embryo implantation and assessment of the transmission of the injected construct is described in the specification, confirmation of the presence of proteins encoded by cDNAs of the

present invention in rat brains is also described, and "experiments assessing phenotypes associated with truncated tau proteins of the present invention are also presented (See, e.g., p. 15, second and third full paragraphs; Figs. 6-8 and 10 and their accompanying descriptions at pp 19-21 and 25; and Example 5 at pp 24-25)". As such applicants contend that there is not undue experimentation required to make and use the present invention in light of the guidance provided in the specification and knowledge available to one of ordinary skill in the art. Such in not persuasive.

The cited pages and paragraphs, particularly on p. 15, second and third full paragraphs; Figs. 6-8 and 10 and their accompanying descriptions at pp 19-21 and 25; and Example 5 at pp 24-25, disclose expression of Alzheimer's tau proteins in the brain of transgenic rats by Western analysis and localizes by immunohistochemistry said proteins in brain tissue sections. Moreover, Fig. 10 shows neurofibrillary tangles similar to those observed in human brain tissue (Example 5). The instant specification is not found fully enabling, because there is not sufficient relevant disclosure of a transgenic rat comprising a N- and C-terminally truncated human tau protein, wherein the cDNA molecule has at least 30 nucleotides downstream of the start codon and truncated at least the 30 nucleotides upstream of the stop codon of the full length tau cDNA sequence said cDNA molecule comprising SEQ ID No. 9, as encompassed in amended claim 17, since the DNA constructs claimed to produce a transgenic rat are not sufficiently disclosed in the as-filed specification other than for disclosure of the truncated human tau protein of SEQ ID No. 9, resulting in the claimed transgenic line #318 phenotype.

Conclusion

Applicant response filed on 01-10-2007 has been considered by the Examiner but is moot in view of the new grounds of the rejection, which is necessitated by the claims amendment.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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